WILSON TURNER KOSMO LLP
Vickie E. Turner (SBN 106431)
550 West C Street, Suite 1050
San Diego, California 92101
Telephone: (619) 236-9600

WILLIAMS & CONNOLLY LLP
Douglas R. Marvin (SBN No. 933671)
F. Lane Heard, III (SBN Bar No. 291724)
Paul E. Boehm (SBN Bar No. 493245)
725 Twelfth Street, N.W.
Washington, D.C. 20005-5901
Telephone: (202) 434-5000

Attorneys for Merck Sharp & Dohme Corp.

DLA PIPER LLP (US)
Loren H. Brown (SBN 2533529)
Heidi Levine (SBN 2822740)
Raymond M. Williams (SBN 164068)
1251 Avenue of the Americas, 27th Floor
New York, NY 10020
Telephone: (212) 335-4500

Attorneys for Novo Nordisk Inc.

PEPPER HAMILTON LLP
Nina M. Gussack (SBN 31054)
Kenneth J. King (SBN 1885961)
3000 Two Logan Square East
Eighteenth and Arch Streets
Philadelphia, PA 19103
Telephone: (215) 981-4000
Facsimile: (215) 981-4750

Attorneys for Eli Lilly and Company

O'MELVENY & MYERS LLP
Richard B. Goetz (SBN 115666)
Amy J. Laurendeau (SBN 198321)
4000 South Hope Street
Los Angeles, CA 90071
Telephone: (213) 430-6000

Attorneys for Amylin Pharmaceuticals, LLC

UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Case No. 13-md-2452-AJB-MDD

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT BASED ON PREEMPTION

Date:	July 3, 2014
Time:	2:00 p.m.
Courtroom:	3B
Judge:	Hon. Anthony J. Battaglia
Magistrate:	Hon. Mitchell D. Dembin

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INTRODUCTION

Plaintiffs claim that defendants failed to provide an adequate warning—specifically, that for each of their medications (Byetta, Januvia, Janumet, and Victoza), defendants failed to warn that the medications (supposedly) cause pancreatic cancer. Federal law, however, preempts state-law claims predicated on failure-to-warn theories where there is clear evidence that the Food and Drug Administration (FDA) would refuse to approve the plaintiff's proposed warning. Here, there can be no doubt that FDA would refuse to approve pancreatic-cancer labeling for Byetta, Januvia, Janumet, and Victoza, because the Agency has said just that—and said it officially—in the *February 2014* issue of *The New England Journal of Medicine* (NEJM)[1] and in its *March 2014* rejection of a Public Citizen Petition.[2]

Having (i) considered the very claim asserted by plaintiffs in this litigation (namely, that the labeling for Byetta, Januvia, Janumet, and Victoza should warn about an increased risk of pancreatic cancer) and (ii) itself conducted a comprehensive evaluation of the scientific evidence concerning pancreatic cancer, (iii) FDA specifically rejected that claim, stating that the scientific data do not support a causal association between the medications and pancreatic cancer, that the current labeling is adequate, and that there is no new evidence that would support a change to the existing labels. In the February 2014 NEJM article, having "committed" itself "to assessing the evidence," FDA concluded:

> [A]ssertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer, as expressed

[1] Amy G. Egan, et al., *Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment*, N. Eng. J. Med. 794 (Feb. 27, 2014) ("FDA/EMA Assessment") (attached as Ex. A to the Declaration of Vickie E. Turner ("Turner Decl.")).

[2] Letter from Janet Woodcock, Dir., FDA Ctr. for Drug Eval. & Research, to Elizabeth Barbehenn & Sidney M. Wolfe, Public Citizen's Health Research Grp. (Mar. 25, 2014) (attached as Ex. B to Turner Decl.).

> recently in the scientific literature and in the media, are *inconsistent* with the current data. . . . . *[T]he current knowledge [regarding safety risks] is adequately reflected in the product information or labeling.*[3]

One month later, FDA restated this endorsement of the adequacy of the current labeling for incretin-based therapies when the Agency rejected a Public Citizen Petition focusing on Victoza. The Petition asked FDA to withdraw Victoza from the market, in part based on a claim that patients being treated with the medication faced an increased risk of pancreatic cancer.[4] As noted in the Agency's March 25, 2014 letter, FDA "carefully considered the information submitted in the Petition, the comments submitted to the docket, and other relevant data identified by the Agency,"[5] and, based on that review, denied the Petition. FDA concluded that the data offered "no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support *any changes to the current approved labeling*."[6]

FDA made these statements summarizing its year-long review of the scientific data and denying the Public Citizen Petition within the last six weeks. The statements represent not only the official position of the Agency, but also the current, scientific consensus, as stated by multiple regulatory, scientific, and professional bodies. There can be no clearer evidence of FDA's determination that the current labeling is

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[3] FDA/EMA Assessment (Ex. A) at 795–96 (emphasis added). The FDA/EMA Assessment refers to the medications in this litigation by their active ingredients, not their brand names: exenatide (Byetta), sitagliptin (Januvia and Janumet), and liraglutide (Victoza).

[4] Letter from Janet Woodcock to Elizabeth Barbehenn & Sidney M. Wolfe (Ex. B) at 26.

[5] *Id.* at 1.

[6] *Id.* at 26 (emphasis added).

adequate, and that the scientific data do not support a pancreatic-cancer label change, than these up-to-the minute official statements of the Agency's position.

THE MATERIAL, UNDISPUTED FACTS

This MDL includes claims involving medications approved by FDA for the treatment of type-2 diabetes. The medications—Byetta, Januvia, Janumet, and Victoza—are broadly referred to as "incretin-based therapies" because they increase the levels of certain incretin hormones, which help lower blood sugar by stimulating production of insulin. More than 25 million people in the United States alone—or just under 1 in 10—suffer from type-2 diabetes.[7]

Incretin-based therapies are an approved treatment option for patients with type-2 diabetes, and all leading medical organizations in the diabetes field recommend them.[8] Medical organizations have recognized the importance of making available a variety of different treatment options because, given the chronic nature of the disease, those suffering from type-2 diabetes often require over time different medications to control their blood sugar.

The medications at issue in this litigation are or at one time were developed and/or distributed by Defendants Amylin Pharmaceuticals, LLC (Amylin), Eli Lilly and Company (Lilly), Merck Sharp & Dohme Corp. (Merck), and Novo Nordisk Inc. (Novo). Amylin manufactures Byetta, which was the first of these medications to obtain FDA approval (approved on April 28, 2005). Lilly previously collaborated with Amylin to promote this medication. Merck manufactures Januvia (approved on

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[7] *See* FDA/EMA Assessment (Ex. A) at 794.

[8] *See* Am. Diabetes Ass'n, *ADA/EASD/IDF Statement Concerning the Use of Incretin Therapy and Pancreatic Disease*, June 28, 2013, at 3 ("ADA/EASD/IDF Statement") (attached as Ex. C to Turner Decl.).

October 16, 2006) and Janumet (approved on March 30, 2007); and Novo manufactures Victoza (approved on January 25, 2010).[9]

Under the Federal Food, Drug, and Cosmetic Act, Congress has committed regulatory authority over the approval and sale of prescription medications to FDA, including considerable authority over the content of prescription medication labeling. 21 U.S.C. § 355(d), (o); 21 C.F.R. pt. 201. Pharmaceutical manufacturers must submit proposed labeling to FDA as part of the new drug-approval process, and FDA must approve any labeling changes that become necessary in light of post-approval studies or experience. 21 C.F.R. § 314.70.

When FDA approved the incretin-based therapies as safe and effective, the Agency necessarily also approved labeling for the medications. Under federal law, a manufacturer cannot warn of suspected risks that are not scientifically substantiated. FDA can only approve a warning as part of the labeling if there is "reasonable evidence" of a causal association between the medication and a particular risk. 21 C.F.R. § 201.57(e).[10] This rule recognizes that "[w]hile it is important for a manufacturer to warn of potential side effects, it is equally important that it not overwarn because overwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted and can dilute the effectiveness of valid warnings."[11] In order to ensure that warnings promote, rather than impede, federal safety goals, FDA has imposed further limits on what may be included. For example:

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[9] *See* FDA Approval Letters for Byetta, Januvia, Janumet, and Victoza (attached as Exs. D, E, F, and G, respectively, to Turner Decl.).

[10] Even to include information about an adverse event in the "Adverse Reactions" section of the label, as opposed to a "Warning," there must be "some basis to believe there is a *causal* relationship" between a medication and that adverse event. 21 C.F.R. § 201.57(c)(7) (emphasis added).

[11] *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) (cited approvingly by *Gaeta v. Perrigo Pharm. Co.*, 630 F.3d 1225, 1235 (9th Cir.), *vacated on other grounds sub. nom. L. Perrigo Co. v. Gaeta*, 132 S. Ct. 497 (2011)).

- "Labeling is not intended to be a dispositive treatise of all possible data and information about a drug." [12]
- Inclusion of statements that "are intended solely to influence civil litigation in which the Agency has no part," "would be inappropriate." [13]
- Inclusion of "substantial differences of opinion among experts" or "other serious medical controversies" concerning labeling statements "would result in uncertainty and confusion, and, accordingly, decrease the usefulness of the warnings in protecting the public." [14]
- Inclusion in "drug labeling of medical or scientific controversy concerning labeling statements would be highly confusing, and thus misleading, in violation of section 502(a) of the act." [15]
- Undesirable effects warned of in the labeling cannot be "coincidental to the use of a drug." [16]

When FDA approved Byetta, Januvia, Janumet, and Victoza, it did not require the labeling for those medications to warn about an increased risk of pancreatic cancer. Nor did the Agency require a pancreatic-cancer warning when it approved each of six other incretin-based therapies as safe and effective medications for the treatment of diabetes, including two approvals in 2014—a new extended release

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[12] Labeling and Prescription Drug Advertising; Content and Format for Labeling for Prescription Drugs, 44 Fed. Reg. 37,434, 37,441 (June 26, 1979).

[13] *Id.* at 37,435.

[14] *Id*. at 37,448.

[15] *Id*. at 37,455; *accord* Labeling: Failure To Reveal Material Facts, 39 Fed. Reg. 33,229, 33,231 (Sept. 16, 1974) ("Although [warnings] are often the subject of intense debate, [FDA] has never permitted drug labeling to reflect such debate."); *see id*. at 33,232.

[16] *Id*. at 37453.

formulation of Bydureon on February 28, 2014, and Tanzeum (albiglutide) on April 15, 2014.[17] And since their initial approval, FDA has repeatedly approved labeling updates for Byetta, Victoza, and Januvia without requiring the manufacturers to provide warnings related to pancreatic cancer. These affirmative decisions to maintain the existing labels followed extensive analysis of whether these medications can cause pancreatic cancer—the specific issue in this litigation.

Beginning no later than 2009, FDA has closely evaluated whether there is a potential risk of pancreatic cancer associated with incretin-based therapies. On September 17, 2009, for example, the FDA Division of Metabolic and Endocrine Products asked the FDA Office of Surveillance and the Epidemiology Division of Pharmacovigilance 1 to review its adverse event reporting database for cases of pancreatic cancer in Januvia and Byetta users.[18] In fulfilling this request, Epidemiology Division searched the database and conducted a literature review using the National Health Institute's database of publications.[19] FDA concluded that "little inference for risk [could be] appreciated from review of spontaneous reports of

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[17] FDA approved Onglyza (saxagliptin) in 2009; Tradjenta (linagliptin) in 2011; Bydureon (extended release exenatide) in 2012; Nesina (alogliptin) in 2013. The FDA Approval Letters for Onglyza, Tradjenta, Bydureon, Nesina, Bydureon (extended release), and Tanzeum are attached as Exs. H, I, J, K, L, and M, respectively, to the Turner Declaration.

[18] *See* Memorandum from John Bishai, Ph.D., Regulatory Project Manager, FDA, DMEP, to Millie Wright, FDA, Office of Safety and Epidemiology, Sept. 17, 2009 (attached as Ex. N to Turner Decl.)

[19] *See* Memorandum from Allen Brinker, Team Leader, FDA Div. of Pharmacovigilance 1, to Mary Parks, Dir., FDA Div. of Pharmacovigilance1, Office of Surveillance & Epidemiology (DPV 1), Dec. 10, 2009 (attached as Ex. O to Turner Decl.).

pancreatic cancer in adult recipients of anti-diabetics agents," because pancreatic cancer is "relatively common" in adults.[20]

One year ago, in March 2013, FDA announced that it would conduct a "comprehensive evaluation" of pancreatic safety issues that were raised about these therapies by a small group of academic researchers at UCLA. FDA said that it would consider the totality of available scientific data, as well as the Agency's own "further investigat[ion] [into the] potential pancreatic toxicity associated with the incretin mimetics."[21] In June 2013, at a public meeting co-sponsored by the National Institute of Diabetes, Digestive and Kidney Diseases and the National Cancer Institute, FDA reviewers shared some of their findings. B. Timothy Hummer, Ph.D., Supervisory Toxicologist, FDA Division of Metabolic and Endocrine Products, stated that "[o]vert pancreatic toxicity or pancreatic neoplasms have not been observed across the [incretin-based] drug classes in [non-clinical testing] that would indicate a risk to human safety."[22] Solomon Iyasu, M.D., M.P.H., FDA Director, Office of Pharmacovigilance and Epidemiology, found that existing adverse event data were

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[20] *Id.* at 8. Again, in 2014, the FDA commented on the limited usefulness of adverse events reports for evaluating a causal association. *See* pp. 9–10, *infra*.

[21] FDA, *FDA Drug Safety Communication: FDA Investigating Reports of Possible Increased Risk of Pancreatitis and Pre-Cancerous Findings of the Pancreas from Incretin Mimetic Drugs for Type 2 Diabetes* (Mar. 14, 2013) ("FDA Review Announcement") (attached as Ex. P to Turner Decl.).

[22] B. Timothy Hummer, *FDA Surveillance of Adverse Drug Effects*, in NIDDK WORKSHOP ON PANCREATITIS-DIABETES-PANCREATIC CANCER PROGRAM BOOK ("NIDDK PROGRAM BOOK") 88, 88 (2013). Dr. Hummer is a co-author of the 2014 NEJM article. Excerpts of the NIDDK PROGRAM BOOK are attached as Ex. Q to the Turner Declaration.

insufficient to conclude that incretin-based therapies present a risk of pancreatic cancer.[23]

On February 27, 2014, the FDA declared that its "comprehensive evaluation" was "now complete," and, in conjunction with the European Medicines Agency (EMA) and Dutch Medicines Evaluation Board, the Agency published its assessment of incretin-based therapies and the risk of pancreatic cancer in NEJM, the oldest peer-reviewed medical journal in the United States,[24] FDA employee co-authors were Amy G. Egan, M.D., M.P.H. (Deputy Director for Safety, Division of Metabolic and Endocrine Products, Center for Drug Evaluation and Research), Dr. Hummer, Todd Bourcier, Ph.D. (Supervisory Pharmacologist/Toxicologist, Division of Metabolic and Endocrine Products), and Curtis Rosebraugh, M.D., Ph.D. (Director, Office of Drug Evaluation).

FDA's publication guidelines establish that an article or speech given by an FDA official is "FDA-Assigned," and thus represents the official position of the agency, unless the article or speech contains a "disclaimer to emphasize that the views expressed in the article or speech do not necessarily represent the official views or policies of the agency."[25] The NEJM article did not contain a disclaimer that the views expressed were not the official views of the Agency. On the contrary, the NEJM identifies the source of the article as "[f]rom the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring,

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[23] Solomon Iyasu, *FDA's Approach to Addressing a Pancreatic Safety Signal with Incretin Memetics*, in NIDDK PROGRAM BOOK (Ex. Q) at 90 (2013).

[24] FDA/EMA Assessment (Ex. A) at 795. Co-authored by scientists from FDA, EMA, and the Dutch Medicines Evaluation Board, the article constitutes their joint assessment of the scientific evidence.

[25] *See* FDA Staff Manual Guide 2126.3, Review of FDA-Related Articles and Speeches § 6.A (attached as Ex. R to Turner Decl.).

MD." And the title is "Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment." The NEJM article describes the "comprehensive evaluations" independently conducted by FDA and EMA in 2013 and concludes:

> Thus, *the FDA* and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. *Both agencies agree that assertions concerning a causal association between incretin-based drugs and* pancreatitis or *pancreatic cancer*, as expressed recently in the scientific literature and in the media, *are inconsistent with the current data*. . . . *The FDA* and the EMA *believe that the current knowledge is adequately reflected in the product information or labeling* . . . .[26]

Less than one month ago, FDA again confirmed that it would not approve pancreatic-cancer labeling for these therapies when it denied a 2012 Petition by Public Citizen asking the Agency to remove Victoza from the market, based in part on the claim that Victoza increases the risk of pancreatic cancer.

As support for its claim, Public Citizen relied on spontaneous adverse event reports of pancreatic cancer compiled in the FDA's adverse event reporting database. But FDA rejected Public Citizen's use of adverse event data to draw valid scientific conclusions about causation. Janet Woodcock, M.D. (Director of FDA's Center for Drug Evaluation and Research) explained in the Agency's March 25, 2014 letter that the data "cannot be used to calculate the incidence of an adverse event in the U.S. population," in particular for events like pancreatic cancer that "occur[] commonly in the background untreated population and ha[ve] a long latency period."[27] The letter further advised Public Citizen that "[t]he safety concerns you raise in the Petition were

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[26] FDA/EMA Assessment (Ex. A) at 796 (emphasis added).

[27] Letter from Janet Woodcock to Elizabeth Barbehenn & Sidney M. Wolfe (Ex. B) at 26, 36.

appropriately and thoroughly considered at the time of initial approval of the Victoza NDA" and concluded that the data offered "no new evidence regarding the risk of pancreatic carcinoma . . . that would support *any changes to the current approved labeling*."[28]

Defendants bring this motion for summary judgment less than one month later.

THE LEGAL STANDARD FOR PREEMPTION

Federal preemption presents a pure question of law, and thus may be resolved on a motion for summary judgment. *See Indus. Truck Ass'n v. Henry*, 125 F.3d 1305, 1309 (9th Cir. 1997); *Dalzin v. Belshe*, 993 F. Supp. 732, 734 (N.D. Cal. 1997) ("It is axiomatic that questions of statutory interpretation [such as preemption] are questions of law" appropriately resolved through summary judgment).[29]

The Supremacy Clause "establishes that federal law 'shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.'" *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2577 (2011) (ellipses in original) (quoting U.S. Const. art. VI, cl. 2). "Even where Congress has not completely displaced state regulation in a specific area," state law is preempted "to the extent that it actually conflicts with federal law." *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982). Such a conflict "arises when compliance with both federal and state regulations is a physical impossibility, or when state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of

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[28] *Id.* at 26, 37 (emphasis added).

[29] Summary judgment is proper, of course, where the factual record shows that there is "no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). Once the moving party meets its initial burden, the burden shifts to the non-moving party to designate specific facts showing that there is a genuine issue for trial. *In re Oracle Corp. Sec. Litig.*, 627 F.3d 376, 387 (9th Cir. 2010).

Congress." *Id.* (citation and internal quotation marks omitted). "Federal regulations" have just as much "pre-emptive effect [as] federal statutes." *Id.*

With respect to product liability litigation involving prescription medications, federal law preempts state law failure-to-warn claims where there is "clear evidence" that FDA would "not have approved" the warning that a plaintiff alleges state law requires. *Wyeth v. Levine*, 555 U.S. 555, 571 (2009).[30] In *Levine*, the inadequate warnings concerned Phenergan, an anti-nausea medication that can be administered intravenously by "IV push" (direct injection into the vein) or by "IV drip" (slow introduction of the medication, as diluted in a saline solution, from a hanging intravenous bag). If the medication enters the artery, it is corrosive and causes irreversible gangrene. Levine suffered gangrene—then amputation—resulting from an IV-push injection of Phenergan. Although the Wyeth labeling warned of the danger of gangrene and amputation from inadvertent intra-arterial injection, Levine alleged that the warning was inadequate because it failed to instruct doctors to use only the IV-drip method. In response, Wyeth argued that the history of its communications with FDA demonstrated that the Agency would not have approved a change in the labeling instructions that cautioned against the IV-push method.

The Supreme Court held that, "absent clear evidence that FDA would not have approved" the proposed warning, there could be no federal preemption. While the court did not define the "clear evidence" standard in a phrase, it did explain why the facts in *Levine* fell short of establishing that the FDA would have rejected the

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[30] *See also, e.g.*, *Mensing*, 131 S. Ct. at 2581 n.8 (explaining that a drug manufacturer may establish a conflict between state and federal law, by "show[ing], by 'clear evidence,' that the FDA would have rescinded any change in the label [made through the CBE process] and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required"); *Dobbs v. Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264 (W.D. Okla. 2011) (post-*Levine* holding that FDA regulations governing the content of prescription drug labeling preempted the plaintiff's common law, failure-to-warn claims).

plaintiff's proposed warning. The Supreme Court found that the almost twenty-year history of sporadic communications between Wyeth and FDA about methods of administering Phenergan did not constitute clear evidence that the Agency would have rejected an instruction that doctors use the IV-drip method exclusively—rather, that FDA gave only "passing attention" to the issue. The Court noted that Wyeth and FDA only "intermittently corresponded about Phenergan's label" over those years.[31] In 1973 and 1976, Wyeth submitted supplemental new drug applications, with labeling changes, which FDA approved. But FDA did not act for seventeen years on Wyeth's third supplemental new drug application, submitted in 1981. In the interval, FDA in 1987 suggested different warnings about the risk of arterial exposure to Phenergan—and Wyeth submitted revised warnings incorporating those suggested changes in 1988—but the "FDA did not respond."[32] Eight years later, the Agency communicated with Wyeth about the labeling then in use, but still failed to address the company's 1981 or 1988 submissions. Only in 1998 did it approve the 1981 submission and instruct Wyeth that the final labeling must be identical to the approved package insert. This was two years before Levine's injury.

The Supreme Court noted approvingly that, based on this factual record, the trial court had "found 'no evidence . . . that either the FDA or the manufacturer gave more than passing attention to the issue of' IV-push versus IV-drip administration" and the Vermont Supreme Court had concluded that "the FDA had not made an affirmative decision to preserve the IV-push method or intended to prohibit Wyeth from strengthening its warning about IV-push administration."[33] The Supreme Court itself observed that Wyeth did not argue that it supplied an "evaluation or analysis" of

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[31] 555 U.S. at 561.

[32] *Id*. at 562.

[33] *Id*. at 572.

the alleged risks of the IV-push method, or that FDA had performed an evaluation or analysis of the scientific data.[34]

Thus, when the Supreme Court held that there was an absence of clear evidence that FDA would have rejected labeling advising against use of the IV-push method, it pointed specifically to the absence of evidence (i) that FDA addressed the specific issue of the relative risk of IV-push versus IV-drip administration of Phenergan, (ii) that FDA considered, or itself made, an evaluation of the scientific data, and (iii) that FDA made an affirmative decision not to authorize the proposed labeling change.

Like *Levine*, the Ninth Circuit in *Gaeta v. Perrigo Pharmaceuticals Co.*, 630 F.3d 1225 (9th Cir. 2011), "defined" what is clear evidence by explaining what evidence does not satisfy that standard.[35] In *Gaeta*, the plaintiffs alleged that the generic manufacturers of ibuprofen failed to warn of the increased risk of acute liver injury and renal failure when ibuprofen is taken concurrently with other drugs known to be hepatotoxic. The defendant countered that this state-law, failure-to-warn claim was preempted, because the FDA considered and rejected the plaintiffs' proposed warning. The district court agreed with the defendant and granted summary judgment on federal preemption grounds.

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[34] *Id*.

[35] In *Gaeta*, the Ninth Circuit held that state law failure-to-warn claims against *generic manufacturers* are not preempted, because (1) a generic manufacturer can utilize the CBE process to make changes to its labeling without prior approval by FDA, and (2) the generic defendant in *Gaeta* had failed to show by "clear evidence" that the FDA would not have approved the labeling change. 630 F.3d at 1235. The Supreme Court vacated the judgment in *Gaeta* in light of *Mensing*, which held that failure-to-warn claims against generic manufacturers *are* preempted. Because *Mensing* held that federal law categorically bars the generic manufacturer from changing the FDA-approved warnings, the Court did not have reason to reach the question whether "clear evidence" showed that FDA would have rejected the plaintiff's proposed warning. *See* 131 S. Ct. at 2581 n.8. Nothing in *Mensing* affects *Gaeta*'s explanation of the "clear evidence" standard.

On appeal, the Ninth Circuit began from the premise that preemption is a viable, if narrow, defense in prescription drug cases: "In *Levine*, the Supreme Court left open the possibility that there could be preemption if a manufacturer was able to demonstrate, by *clear evidence*, that the FDA would not have approved the change to the drug's label proposed by the plaintiff."[36] The Ninth Circuit then looked to the evidence found insufficient in *Levine* for guidance as to what would constitute "clear evidence." Specifically, the court noted three central shortcomings in the evidence cited by Wyeth in *Levine*: (i) that the evidence reflected that FDA gave only "passing attention" to the precise issue of IV-push versus IV-drip, (ii) that FDA did not make or consider "an evaluation or analysis" of the risks at issue, and (iii) that FDA did not make a definitive decision, as it "apparently 'did not regard the proposed warning as substantively different' from the FDA-approved warning."[37]

The *Gaeta* court found these same shortcomings in the evidence provided by defendant Perrigo. First, although the Agency in earlier years had made a detailed review of the overall safety (including the risk of hepatotoxicity) of ibuprofen, "[n]owhere does [the defendant] point to any evidence that the FDA was presented with and actually considered the risk of hepatotoxicity due to concomitant use of ibuprofen and other medications known to be hepatotoxic, which was the specific warning requested by the Gaetas in this case."[38] Second, the defendant offered no evidence that "it supplied the FDA with any 'evaluation or analysis concerning the specific dangers' posed by such concomitant use." And, accordingly, third, the

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[36] *Gaeta*, 630 F.3d at 1235.

[37] *Id*. at 1236 (quoting *Levine*, 555 U.S. at 572 n.5).

[38] *Id*. at 1237.

defendant offered no evidence that "the FDA refused to act" in light of such an evaluation and analysis.[39]

Thus, in determining whether "clear evidence" exists, the Court should begin with a comparison to the facts of *Levine* and should then examine FDA's analysis of the specific warning at issue in the case. The ultimate inquiry is whether, given the requirement that there be "reasonable evidence of a causal association" with the medication and a "clinically significant hazard," there is "clear evidence" that FDA would have rejected the specific warning at issue.

ARGUMENT

A. Under the Guidelines for "Clear Evidence" Provided by *Levine*, Plaintiffs' Failure-To-Warn Claims Are Preempted.

In March 2013, FDA announced that it would conduct a "comprehensive evaluation" of a possible association between incretin-based medications and pancreatic cancer and that it would consider the entire body of scientific research and data available to date, as well as the Agency's own "further investigat[ion] [into the] potential pancreatic toxicity associated with the incretin mimetics."[40] In that March 2013 statement, FDA noted that it would "evaluate all available data to further understand this potential safety issue":

> The U.S. Food and Drug Administration (FDA) is evaluating unpublished new findings by a group of academic researchers [the Butler Group] that suggest an increased risk

[39] *Id*. FDA did later require the very warning sought by the plaintiffs for prescription-strength ibuprofen. The defendant argued that this fact implied a calculated decision not to require the same warning for over-the-counter ibuprofen. But the court said that "the conclusion to be drawn from this is quite the opposite: the fact that FDA later required these liver warnings on prescription-strength ibuprofen suggests that FDA might also have accepted similar warnings for the OTC ibuprofen had [the defendant] suggested such warnings." *See id.* n.10.

[40] FDA Review Announcement (Ex. P).

> of pancreatitis, or inflammation of the pancreas, and pre-cancerous cellular changes called pancreatic duct metaplasia in patients with type 2 diabetes treated with a class of drugs called incretin mimetics. . . . FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and health care professionals that the Agency intends to obtain and evaluate this new information. FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report. . . . *FDA is continuing to evaluate all available data to further understand this potential safety issue. In addition, FDA will participate in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute's (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June 2013 to gather and share additional information.*[41]

The publication in NEJM of "Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment" in February 2014 reflects the result of that evaluation—an evaluation that FDA describes as "comprehensive."[42] The Agency's year-long evaluation of a possible association between incretin-based therapies and pancreatic cancer included the following components:

- FDA performed its own independent pancreatic toxicology studies with Byetta, using three different rodent models of disease accompanied by a non-diseased control. Data from two models showed no drug-related pancreatic injury; from the third, "minimal-to-moderate" exacerbation of certain pancreatic background effects.[43]

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[41] *Id*. (emphasis added).

[42] FDA/EMA Assessment (Ex. A) at 796.

[43] *Id.* at 795–96.

- FDA "re-evaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals." These studies showed "no findings of overt pancreatic toxic effects . . . ." The Agency also found that "drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to 2 years (their life span) with incretin-based drugs, even at doses that greatly exceed the level of human clinical exposure."[44]
- FDA required the manufacturers of incretin-based medications to conduct "3-month pancreatic toxicity studies in a rodent model of diabetes," which studies included "extensive" histopathological evaluation of the endocrine and exocrine pancreas. The studies showed "no treatment-related adverse effects on the pancreas were reported."[45]
- FDA subjected 120 pancreatic histopathology slides from one of these 3-month studies to "independent and blinded examination by three FDA pathologists," whose conclusions were "generally concordant" with the sponsors' conclusions.[46]
- FDA reviewed the safety data from more than 200 clinical trials, involving approximately 41,000 participants, more than 28,000 of whom used an incretin-based therapy. 15,000 of these participants used an incretin-based therapy for 24 weeks or more; 8500, for 52 weeks or more.[47]
- FDA reviewed a manufacturer-sponsored pooled analysis of data from 14,611 patients with type-2 diabetes from 25 clinical trials in the Januvia/Janumet

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[44] *Id*. at 795.

[45] *Id.*

[46] *Id.*

[47] *Id*. at 796.

database and concluded that it "provided no compelling evidence of an increased risk of pancreatitis or pancreatic cancer."[48]

- FDA also examined safety data from two large, cardiovascular-outcome trials (the SAVOR and EXAMINE trials), which were conducted in patients with type-2 diabetes who were using two incretin-based therapies that are not a part of this MDL (Onglyza and Nesina).
  - The SAVOR trial was a randomized, double-blind, placebo-controlled trial involving 16,492 patients. The reported incidence of pancreatic cancer in SAVOR was: 5 in the group of patients treated with Onglyza versus 12 in the group of patients treated with placebo.[49]
  - The EXAMINE trial was a randomized, double-blind, placebo-controlled trial involving 5,380 patients. There was no incidence of pancreatic cancer reported in either the Nesina or the placebo group.[50]

It was on the basis of this year-long evaluation and analysis that FDA said that "assertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer, as expressed recently in the scientific literature and in the media, are *inconsistent* with the current data" and that "the current knowledge is *adequately* reflected in the product information or labeling."[51]

One month later FDA rejected a petition to withdraw Victoza from the market, noting that there was "no new evidence regarding the risk of pancreatic carcinoma . . . *that would support any changes to the current approved labeling*."[52] With FDA's

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[48] *Id.*

[49] *Id.*

[50] *Id.*

[51] FDA/EMA Assessment (Ex. A) at 796 (emphasis added).

[52] Letter from Janet Woodcock to Elizabeth Barbehenn & Sidney M. Wolfe (Ex. B) at 26 (emphasis added).

affirmative rejection of "*any changes*"[53] to the existing Victoza label, the Agency delivered additional "clear evidence" that it does not approve of a pancreatic cancer warning for the products in the class.

FDA's position regarding a pancreatic cancer warning is current, clear, and specific to the issue raised in the litigation. Having (i) considered the very claim asserted by plaintiffs in this litigation, and (ii) itself conducted a comprehensive evaluation of the scientific evidence concerning the alleged risk of pancreatic cancer, (iii) FDA concluded that the scientific data do not support label changes. There can be no clearer demonstration that FDA thoroughly considered the relevant safety issue and made a determination that the available data do not merit a pancreatic cancer warning.

In *Levine*, FDA appeared to give only "passing attention" to the issues surrounding the relevant safety question, and the Agency's last word on the subject was two years before the plaintiff's injury. In *Gaeta*, FDA never addressed the issue of liver injury from concomitant use of ibuprofen and other hepatotoxic medications in any way, much less carried out an evaluation and analysis of the risks of concomitant use. Here, however, FDA's year-long efforts in evaluating whether an increased pancreatic cancer risk is associated with use of incretin-based therapies reflects a level of attention and activity that is at the other end of the continuum from *Levine* and *Gaeta*.[54] FDA has devoted several years to evaluation and analysis of both

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[53] *Id.* (emphasis added).

[54] The facts here are similar to those in *Dobbs v. Wyeth*, where the court found that FDA had given more than "passing attention" to the risk at issue and would have rejected the plaintiff's proposed warning. The court found specifically that (i) "despite its continuing review of [the drug] manufacturers' periodic reports of clinical trials and adverse events, the FDA continued to find no scientific evidence of a causal connection between [the drugs] and increased suicidality warranting an enhanced warning," (ii) rejected a series of citizen petitions, and (iii) for a series of supplemental New Drugs Applications "directed Wyeth to include the same language

the science and labeling for these products. FDA's announcements, first in February 2014—less than two months ago—that the labeling adequately reflects the current scientific knowledge about the risks of incretin-based therapies, and next in March 2014, rejecting the Public Citizen Petition to withdraw Victoza from the market (and stating that there is no new evidence to support pancreatic-cancer labeling) is "clear evidence" that the Agency would reject a label change for pancreatic cancer.[55] These official investigations and conclusions are precisely the sort of "clear evidence" of FDA involvement and decision making contemplated by *Levine*.

Furthermore, there is no question that these communications represent official FDA considerations and clear responses to the failure-to-warn allegations in this litigation. Four of the February 27, 2014 NEJM article authors are FDA officials in the Center for Drug Evaluation and Research (including the Director of the Office of Drug Evaluation and the Deputy Director of the Division of Metabolic and Endocrine Products, Center for Drug Evaluation and Research); the title of the article reflects that it is an "FDA and EMA Assessment"; the article contains no disclaimer (indeed, it notes that it is "[f]rom the Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration"); and the article is replete with statements about "the FDA's" position on the issues. Likewise, the March 25, 2014 letter rejecting the April 2012 Public Citizen Petition related to Victoza plainly reflects an FDA-authorized investigation and response, authored by Janet Woodcock, M.D. (Director of FDA's Center for Drug Evaluation and Research).

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as appeared in the [original] label warnings regarding suicide." *Dobbs*, 797 F. Supp. 2d at 1272–73. The court found that FDA's attention to the issue continued even after the plaintiff's death, for the agency rejected an enhanced warning for pediatric users that Wyeth had unilaterally implemented. *Id.* at 1276.

[55] Letter from Janet Woodcock to Elizabeth Barbehenn & Sidney M. Wolfe (Ex. B) at 26; FDA/EMA Assessment (Ex. A) at 796.

B. FDA's Evaluation and Analysis Reflects the Current Scientific Consensus.

FDA's determination that the data do not support a causal association between incretin-based therapies and pancreatic cancer, reached after a thorough evaluation and analysis, accords with the scientific consensus of other regulatory bodies and professional associations. The fact that FDA's careful evaluation of the scientific data comes to the same conclusion as the recent evaluations made by other bodies is further evidence that the Agency gave serious attention to the issue and that FDA would reject any labeling for pancreatic cancer.

The European Medicines Agency Report. In 2013, EMA reviewed all of the preclinical (animal) and clinical (human) data on incretin-based therapies, and convened a group of distinguished experts to consider the safety of the incretin-based therapies "further to the findings by a group of academic researchers [the Butler Group] suggesting an increased risk of pancreatitis and cellular changes in patients treated for [Type-2 diabetes] with GLP-1 based therapies."[56] EMA evaluated Dr. Butler's organ donor study,[57] then thoroughly reviewed and summarized the preclinical and clinical data for each incretin-based therapy "with a focus on pancreatitis and/or pancreatic cancer."[58] EMA reached and published the following conclusions:

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[56] European Medicines Agency, *Assessment Report for GLP-1 Based Therapies* (July 25, 2013) ("EMA Report") at 4 (attached as Ex. R to Turner Decl.).

[57] Alexandra E. Butler, et al., *Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors*, Diabetes 62:2595–2604 (2013) (attached as Ex. S to Turner Decl.).

[58] EMA Report (Ex. R) at 7.

- "With respect to nonclinical data, *available studies previously submitted for the approved products have not raised concern with respect to pancreatic safety*. Further, published studies have not shown any evidence for treatment-related pancreatitis or preneoplastic [i.e., pre-cancerous] lesions . . . ."
- "Concerning pancreatic cancer, *there is currently no support from clinical trials that GLP-1 based therapies increase the risk*."
- "[T]he randomised, controlled nature of the clinical studies gives a robust estimate of risk in relation to placebo and other treatments. *The data currently available from clinical trials do not indicate an increased risk for pancreatic cancer with these medicines*."[59]

The American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation, NCI, and NIDDK. In June 2013, the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases convened a joint conference of leaders in the fields of diabetes and pancreatic cancer.[60] The conference addressed whether there is evidence that incretin-based therapies cause or increase the risk for pancreatic cancer. Following the NCI/NIDDK conference, the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the International Diabetes Federation (IDF) issued a joint statement which reported that the scientific evidence reviewed at the workshop provided "no concerns for pancreatic disease."[61] The ADA, EASD, and IDF all affirmed their recommendation of incretin-based therapies as an important option for patients with diabetes.

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[59] *Id.* at 15, 16 (emphasis added).

[60] *See* Nat'l Inst. of Diabetes & Digestive & Kidney Diseases, *NIDDK-NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer*, http://www2.niddk.nih.gov/News/Calendar/PDPC2013.htm (last visited Apr. 17, 2014).

[61] ADA/EASD/IDF Statement (Ex. C) at 1.

Endocrinologists. On August 20, 2013, the American Association of Clinical Endocrinologists and the American College of Endocrinology issued a Consensus Statement on the relationship between diabetes and cancer. The organizations acknowledged Dr. Butler's "speculations about the theoretical possibility of increased incidence of pancreatic cancer" arising from incretin-based therapies, but concluded that the risk has not been proven. "[N]o randomized controlled prospective human study of [incretin-based therapies] has conclusively shown that these drug classes play a role in the genesis of pancreatic cancer," the statement noted, and it summarized the data in these words: "No evidence of . . . pancreatic cancer in humans."[62]

FDA will not approve a warning unless "reasonable evidence of a causal association" between the disease and the medication supports the warning. 21 C.F.R. § 201.57(c)(6)(i); *see also Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010).[63] Indeed, it is "a violation of federal law" for a manufacturer to propose the addition of a warning to a label "that is not based on reasonable evidence." *Id.* FDA defines "reasonable evidence" as "evidence . . . on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug."[64] FDA's conclusion in February-March 2014, based on its up-to-the-minute review of the scientific data, is that such reasonable evidence of a causal association between incretin-based therapies

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[62] Yehuda Handelsman, et al., *Diabetes and Cancer—An AACE/ACE Consensus Statement*, 19 ENDOCRINE PRACTICE 675, 685, 687 (2013) (attached as Ex. T to Turner Decl.).

[63] In 2006, the FDA recodified § 201.57(e) as § 201.57(c)(6)(i), without comment, as part of that codification the FDA added the adjective "causal" before "association." Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,922, 3,990 (Jan. 24, 2006).

[64] Labeling and Prescription Drug Advertising: Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979).

and pancreatic cancer does not exist. That the larger scientific community agrees with FDA only confirms that the Agency would not approve a label change for pancreatic cancer.

CONCLUSION

It is now a legal chestnut that "[l]aw lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). The law can only address what is true ***now***. What lies in the future is a matter for conjecture. The ***clear evidence*** is that, here and now, FDA would not approve pancreatic-cancer labeling for these products. Therefore, federal law preempts plaintiffs' failure-to-warn claims.

Respectfully submitted,

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WILSON TURNER KOSMO LLP

By: s/ Vickie E. Turner
Vickie E. Turner (SBN 106431)
E-mail: vturner@wilsonturnerkosmo.com

WILLIAMS & CONNOLLY LLP
Douglas R. Marvin (D.C. Bar No. 933671)
F. Lane Heard, III (SBN Bar No. 291724)
Paul E. Boehm (D.C. Bar No. 493245)
E-mail: dmarvin@wc.com
Email: lheard@wc.com
E-mail: pboehm@wc.com

Attorneys for Merck Sharp & Dohme Corp.

Dated: April 17, 2014

DLA PIPER LLP (US)

By: s/ Loren H. Brown
Loren H. Brown (SBN 2533529)
Heidi Levine (SBN 2822740)
Raymond M. Williams (SBN 164068)
Email: loren.brown@dlapiper.com
Email: heidi.levine@dlapiper.com
Email: raymond.williams@dlapiper.com

Attorneys for Novo Nordisk Inc.

Dated: April 17, 2014

O'MELVENY & MYERS LLP

By: s/ Richard B. Goetz
Richard B. Goetz (SBN 115666)
Amy J. Laurendeau (SBN 198321)
Email: rgoetz@omm.com
Email: alaurendeau@omm.com

Attorneys for Amylin Pharmaceuticals, LLC

Dated: April 17, 2014

PEPPER HAMILTON LLP

By: s/ Kenneth J. King
Nina M. Gussack (SBN 31054)
Kenneth J. King (SBN 1885961)
Email: gussackn@pepperlaw.com
Email: kingk@pepperlaw.com

Attorneys for Eli Lilly and Company

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Pursuant to Section 2.f.4 of the Court's CM/ECF Administrative Policies, I hereby certify that authorization for the filing of this document has been obtained from each of the other signatories shown above and that all signatories have authorized placement of their electronic signature on this document.

By: s/ Vickie E. Turner
Vickie E. Turner